Fibrous dysplasia

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Chapter 12

Summary of this thesis

Fibrous dysplasia (FD) is a rare and ubiquitous disorder, with a very wide clinical spectrum, not only related to the different distribution and evolution of skeletal lesions over time, and the variable related symptoms and impairment in function and quality of life, but also to the wide potential range of extra-skeletal manifestations possibly present in these patients: no two fibrous dysplasia patients are alike. This thesis addresses the heterogeneity of FD, grouping the study of interesting and important topics and issues related to this disorder in four parts: Pain and quality of life; Extra-skeletal manifestations, Surgical treatment and Medical treatment.

Part I: Pain and quality of life in fibrous dysplasia

Part I of this thesis addresses the consequences of having fibrous dysplasia on various aspects of quality of life. In **Chapter 2** FD-associated pain symptoms were evaluated in a collaborative study between the Medical University of Graz and the Leiden University Medical Center. A total of 197 patients with FD completed a survey about the presence and severity of pain at the site of their FD lesions. Mean reported pain score on a scale of 1–10 was 1.9 in the whole group and 4.1 in patients who reported having pain. The severity of pain was significantly higher in patients with lesions of the lower extremities or ribs compared to patients with lesions of the upper extremity or with craniofacial lesions. The presence of pain did not significantly differ between localizations of FD lesions. Severe subtypes of FD (polyostotic/McCune Albright) were associated with both presence and severity of pain. Although less than 50% of patients with FD reported pain at the site of their lesions, pain represented a major clinical manifestation of the disorder, also in limited monostotic disease. These results provide new insights in our appreciation of pain in FD.

In **Chapter 3** quality of life and pain levels were evaluated in 97 patients with FD, using the Short Form-36 and the Brief Pain Inventory questionnaires. Data were compared with those of the general Dutch population. Fibrous dysplasia patients had significantly lower quality of life outcome scores compared to the general Dutch population in all tested domains of the Short Form-36 except for the "Mental health" and the "Role emotional" domains. Severe type of FD was associated with more impaired quality of life outcomes. There was no significant difference in Brief Pain Inventory domains between FD subtypes. Quality of life was lower in patients with high skeletal disease burden, as reflected by high skeletal burden scores and high levels of the bone turnover marker P1NP. We demonstrated impairments in quality of life across the wide spectrum of FD, which importantly also includes its milder monostotic forms. These findings hold significant clinical implications as they draw attention to the clinically

unmet need to address Quality of Life issues in the management of patients with all types of FD, including its monostotic forms.

In **Chapter 4**, Illness Perceptions were studied in our cohort of FD patients. Illness perceptions are patients' cognitions and emotions about their illness and its treatment, which may importantly impact on Quality of Life. Illness perceptions were compared between patients with FD and those with other disorders; factors associated with illness perceptions were identified and their relationship with Quality of Life evaluated. A difference in illness perceptions was observed between FD subtypes and interestingly, patients with craniofacial lesions reported perceiving more consequences of their illness than those with other FD localizations. High skeletal burden score was associated with perceiving more negative consequences of the disease and attributing the cause of FD to psychological factors. High FGF-23 levels were associated with attributing more symptoms to the disease and perceiving more consequences. The majority of IPQ-R domains were associated with impairments in Quality of Life. Our results demonstrate that in patients with FD illness perceptions importantly relate to Quality of Life, differ from those in patients with other disorders, and are associated with disease severity. Identifying and addressing maladaptive illness perceptions may improve the quality of life in patients with FD.

Part II: Extra-skeletal manifestations of fibrous dysplasia

Part II of this thesis addresses extraskeletal manifestations in patients with FD, which are important to screen for the full evaluation of the spectrum of the disorder. Intramuscular myxomas in the context of Mazabraud's syndrome represent a rare, but one of the most well-known non-endocrinological manifestations of *GNAS*-mutations outside the skeleton in FD. In **Chapter 5**, the clinical course, treatment outcomes and role of *GNAS*-mutations was evaluated in patients with the Mazabraud's syndrome in a multi-centre study conducted under the auspices of the European Musculo-skeletal Oncology Society (EMSOS). In a combined cohort of 32 patients a prevalence of Mazabraud's syndrome of 2.2% was observed among all types of FD patients, including those with monostotic disease. However, this may still be an underestimate of the true prevalence of myxomas in FD due to the often-asymptomatic nature of intramuscular myxomas. Patients with disproportional complaints or persistent resistance to treatment of pain symptoms should therefore undergo further evaluation, preferably with MR-imaging as these symptoms might be soft tissue related. We also demonstrated that although surgical resection results in satisfactory outcomes, a quarter of the patients require further surgery despite

free resection margins. High cellularity of the myxomas was identified as a risk factor for recurrence after resection. Finally, *GNAS*-mutations were identified in 83% of the resected myxomas tested, emphasising the shared origin of FD and myxomas and the fact that the *GNAS*-mutation is capable of causing lesions outside the skeleton in patients with FD. Specific attention was also reserved for the role of *GNAS*-mutations in **Chapter 6**, addressing the finding of an increased risk in women with FD to develop breast cancer. In a combined study with the National Institutes of Health in Bethesda (US), the incidence of breast cancer was shown to be higher in women with FD compared to the incidence in the respective national populations of the Netherlands and the US, and women who developed breast cancer were shown to develop the malignancy at a younger age than that of the general population. These findings were confirmed by data from the National Dutch Pathology Registry. Data from this study further showed that the risk of developing breast cancer in FD was especially increased in women with FD lesions of the thoracic region, in the proximity of the breast. This was emphasized by the finding of a *GNAS*-mutation in 44% of the breast cancers studied, while these mutations are normally found in less then 1% of breast cancers in the general population. Although this is the first study addressing the prevalence of breast cancer in FD, we believe our results to be substantial enough to recommend early screening for breast cancer in women with FD, especially in those with thoracic FD lesions.

Part III: Surgical treatment of fibrous dysplasia

In **Chapter 7** the role of allogeneic strut grafts was evaluated in patients with FD lesions of the proximal femur. In a series of 28 patients we showed that revision surgery was indicated in 46% of the patients, mainly because of resorption of the graft. However, we were able to identify specific risk factors for failure of allogeneic graft surgery, including a preoperative fracture of the proximal femur and insufficient proximal anchoring of the graft in healthy bone. In patients without these risk factors, allogeneic strut grafting offers a viable option with good outcomes. Patients who do have risk factors for failure should be treated with osteosynthesis instead of grafting. This was further evaluated in **Chapter 8**, where the outcomes of intramedullary nailing and angled blade plates were evaluated in 32 patients from a combined cohort of the Leiden University Medical Center and the Medical University of Graz. Revision-free survival was 72% after a median follow-up of 4.1 years, and only two patients had structural failure, both having been treated with an angled blade plate and having developed a fracture below the angled blade plate in the area of an FD lesion. Seven patients with complaints of the iliotibial tract had their angled blade plates removed without further complications.

The majority of the patients showed good outcomes regarding levels of pain, function and femoral-neck-shaft-angle. It was therefore concluded that FD of the proximal femur can be adequately and safely treated with angled blade plates or intramedullary nails, provided that these are used according to specific characteristics of the individual patient. On the basis of these results combined with data from published literature, an individualized, patient-tailored approach to the surgical management of FD of the proximal femur was proposed taking into account different treatment modalities and associated factors potentially playing a role in the outcome of the different implants. In the last chapter on the surgical management of FD, **Chapter 9**, findings from a study of 50 patients with FD lesions of the humerus are reported. Data showed that although FD of the humerus generally runs a mild course, over half of the patients had sustained a fracture. Interestingly, cystic degeneration, and not the size of the lesion, was identified as a risk factor for fractures. As cystic degeneration of FD appears to have a direct effect on its course, further evaluation of lesions at this site should be performed using MR-imaging, as cysts cannot be reliably evaluated on conventional radiographs. We stated that pathological fractures of the humerus may be safely treated conservatively in FD, as we demonstrated good outcomes in two thirds of patients who had conservative treatment of these fractures. Outcome of surgical treatment in an attempt to decrease pain or stabilize impending fractures might benefit from the use of cortical grafting instead of cancellous bone grafting, although definitive recommendations on the best surgical interventions should await results of future studies conducted in larger cohorts.

Part IV: Medical treatment of fibrous dysplasia

In **Chapter 10** the results of long-term treatment of patients with polyostotic FD with or without additional endocrinopathies in the context of McCune-Albright syndrome (MAS) with bisphosphonates are presented. Outcomes of treatment with these agents including biochemical outcome (change in bone turnover markers) and clinical outcome (pain reduction) of bisphosphonate therapy were evaluated in 11 patients with MAS and 30 patients with polyostotic FD after a median duration of treatment of 6 years. Twenty-four of 30 patients with polyostotic disease (80%) demonstrated a complete clinical and biochemical response within a year of starting treatment, compared to only four of 11 MAS patients (36%). There were no non-responders. In the whole group, FGF-23, total ALP, P1NP, and CTX positively correlated with skeletal burden scores, which was the only significant risk factor for an incomplete response to bisphosphonate therapy. Our data suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with polyostotic FD, although

response to therapy was limited by the higher skeletal disease burden in MAS patients. In the population studied, the only identified prognostic factor that influenced the outcome of bisphosphonate therapy was a high skeletal burden score, suggesting that in more severely affected patients, the effect of bisphosphonates might be insufficient. In **Chapter 11**, treatment outcomes of denosumab, a monoclonal antibody to RANK-L were evaluated in 12 bisphosphonate-refractory patients with a median follow-up of 14.5 months. This is the first report of denosumab outcomes in a series of patients with FD. Denosumab was administered by subcutaneous injections of 60 mg 3–6 monthly on the basis of high bone turnover with associated complaints of pain. Patients with a 3-monthly treatment schedule had significantly more decrease in bone turnover markers compared to patients on a 6-monthly treatment schedule. BTM normalized in 8 of the 12 patients, 5 of whom had not reached normalisation of BTM after long-term treatment with bisphosphonates. Denosumab was well tolerated and no side effects were reported. Our results show that denosumab may provide a well-tolerated and effective therapeutic option in patients with severe FD refractory to treatment with bisphosphonates. Three-monthly 60 mg dosage schemes appear to have the most promising effect on bone turnover markers and pain.